(12) UK Patent Application (19) GB (11) 2 158 440 A

(43) Application published 13 Nov 1985

(21) Application No 8514278

(22) Date of filing 6 Jun 1985

(30) Priority data
(31) 8501542 (32) 22 Jan 1985 (33) GB

(51) INT CL⁴
C07D 471/04 A61K 31/435 // (C07D 471/04 221/00 233/00)

(52) Domestic classification
C2C 1230 1420 1626 214 215 220 226 22Y 247 250 252 25Y 280 281 282 30Y 313 31Y 338 342 34Y 351 355 35X 364 366 367 368 36Y 368 387 388 389 401 40Y 491 493 574 594 624 625 628 62X 638 65X 662 675 678 699 802 80Y AA BC KF KK UJ
U1S 2410 C2C

(56) Documents cited
None

(58) Field of search
C2C

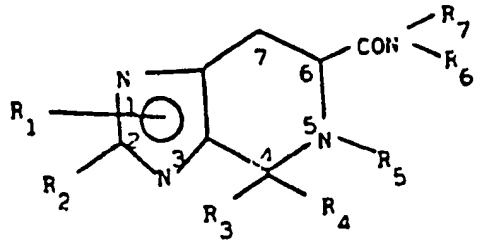
(71) Applicant
Farmitalia Carlo Erba S p A (Italy),
Via Imbonati 24, 20159 Milano, Italy

(72) Inventors
Ugo Scarponi
Roberto Cimaschi
Roberto De Castiglione
Antonietta Verini

(74) Agent and/or Address for Service
J A Kemp & Co,
14 South Square, Gray's Inn, London WC1R 5EU

(54) 4,5,6,7-Tetrahydroimidazo[4,5-c]pyridine derivatives

(57) This invention relates to a 4,5,6,7-tetrahydroimidazo[4,5-c]pyrimidine derivative of general formula (I):



(I)

wherein

$-R_1$, which is bonded to the nitrogen atom in the 1- or 3-position, is a hydrogen atom; a linear or branched C_1–C_4 alkyl or C_2–C_4 alkenyl group; or a benzyl group optionally substituted by one or two substituents selected from a) C_1–C_4 alkoxy, b) C_1–C_4 alkylthio, c) fluorine, d) chlorine, e) bromine, f) trifluoromethyl, g) nitro, and h) methylendioxy;

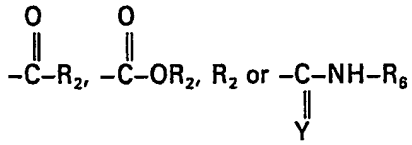
$-R_2$, R_3 and R_4 are independently hydrogen; a linear or branched C_1–C_4 alkyl or C_2–C_4 alkenyl group; a C_3–C_7 cycloalkyl group; a phenyl or benzyl group optionally substituted by one or two substituents selected from a) to h) as defined above; or R_3 and R_4, together with the the carbon atom to which they are attached, form a C_3–C_7 ring;

$-R_6$ and R_7 are independently hydrogen; a linear or branched C_1–C_4 alkyl or C_2–C_4 alkenyl group; a C_3–C_7 cycloalkyl group; a phenyl or benzyl group optionally substituted by one or two substituents selected from a) to h) as defined above; an adamantyl or an adamantanemethyl group; or R_6 and R_7, together with the nitrogen atom to which they are attached, form a five-, six- or seven membered heterocycic ring which may contain one or more other heteroatom selected from O and NR_2 wherein R_2 is as defined above; and

$-R_5$ represents a group of formula

Continued overleaf . . .

GB 2 158 440 A



wherein R_2 is as defined above but is not a phenyl group when R_5 is R_2, and Y represents an oxygen or sulphur atom; to the pharmaceutically acceptable and addition salts thereof and to a process for their preparation.

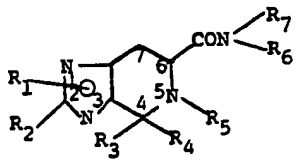
The compounds have anti-viral activity.

SPECIFICATION

4,5,6,7-Tetrahydroimidazo[4,5-c]pyridine derivatives

This invention relates to 4,5,6,7-tetrahydroimidazo[4,5-c]pyridine derivatives, to their preparation and to pharmaceutical compositions containing them.

The present invention provides 4,5,6,7-tetrahydroimidazo[4,5-c]pyridine derivatives of general formula (I):



(I)

wherein

—R_1, which is bonded to the nitrogen atom in the 1- or 3-position, is a hydrogen atom; a linear or branched C_1–C4 alkyl or C_2–C_4 alkenyl group; or a benzyl group optionally substituted by one or two substituents selected from a) C_1–C_4 alkoxy, b) C_1–C_4 alkylthio, c) fluorine, d) chlorine, e) bromine f) trifluoromethyl, g) nitro and h) methylendioxy;

—R_2, R_3 and R_4 are independently hydrogen; a linear or branched C_1–C_4 alkyl or C_2–C_4 alkenyl group; a C_3–C_7 cycloalkyl group; a phenyl or benzyl group optionally substituted by one or two substituents selected from a) to h) as defined above; or R_3 and R_4, together with the carbon atom to which they are attached, form a C_3–C_7 ring;

—R_6 and R_7 are independently hydrogen; a linear or branched C_1–C_4 alkyl or C_2–C_4 alkenyl group; a C_3–C_7 cycloalkyl group; a phenyl or benzyl group optionally substituted by one or two substituents selected from a) to h) as defined above; an adamantyl or an adamantanemethyl group; or R_6 and R_7, together with the nitrogen atom to which they are attached, form a five-, six- or seven-membered heterocyclic ring which may contain one or more other heteroatom selected from O and NR_2 wherein R_2 is as defined above; and

—R_5 represents a group of formula

$$-\overset{\overset{O}{\|}}{C}-R_2,\quad -\overset{\overset{O}{\|}}{C}-OR_2,\quad R_2 \text{ or } -\overset{\overset{Y}{\|}}{C}-NH-R_6$$

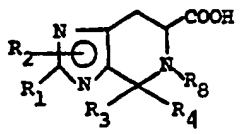
R_2 is as defined above but is not a phenyl group when R_5 is R_2, and Y represents oxygen or sulphur atom; and pharmaceutically acceptable acid addition salts thereof.

The configurations of the carbon atoms in position 4 and 6 (see formula (I)) are independently R or S, so that the stereochemistry of the final products (I) can be RR, SS, RS or SR; or the final products (I) can be mixtures of diastereoisomers, or even racemic mixtures.

Preferably, R_1 and R_2 independently represent a hydrogen atom or a methyl, ethyl, n-propyl, i-propyl, n-butyl, sec-butyl or i-butyl group;
R_3 and R_4 independently represent a hydrogen atom or a methyl, ethyl, n-propyl, i-propyl, n-butyl, sec-butyl, i-butyl, phenyl (optionally para-substituted by a methoxy or nitro group) group or, taken together, represent a cyclohexane or cyclopentane ring;
R_5 represents a hydrogen atoms or a methyl, ethyl, n-propyl, i-propyl, n-butyl, sec-butyl, i-butyl, benzyl or benzyloxycarbonyl (either optionally being para-substituted by a methoxy or nitro group), benzoyl, butyryl, acetyl, propionyl, allyloxycarbonyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl, methylaminothiocarbonyl, ethylaminothiocarbonyl or propylaminothiocarbonyl group; and
R_6 and R_7 independently represent adamantyl, adamantanemethyl, hydrogen, phenyl (optionally substituted by fluorine, methoxy or trifluoromethyl) or, taken together, form a piperazino ring substituted by phenyl, p-methoxyphenyl or p-chlorophenyl or a morpholino ring.

More preferably, R_1 and R_2 represent hydrogen, one of R_3 and R_4 represents ethyl or hydrogen and the other represents hydrogen, R_5 represents hydrogen, methyl, unsubstituted benzyl or benzyloxycarbonyl, and one of R_6 and R_7 represents adamantyl, adamantanemethyl, unsubstituted phenyl or hydrogen and the other represents hydrogen or R_6 and R_7, together with the nitrogen atom to which they are attached, form a piperazino ring substituted by phenyl, p-methoxyphenyl or p-chlorophenyl.

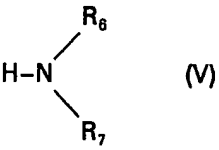
The present invention also provides a process for preparing a compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof, which process comprises reacting a compound of formula (IV) or a reactive derivative thereof, such as a reactive ester, optionally generated *in situ* by reaction with an activating agent:



(IV)

wherein R_1, R_2, R_3 and R_4 are as defined above and R_8 represents a linear or branched C_1–C_4 alkyl or C_2–C_4 alkenyl group, a C_3–C_7 cycloalkyl group, a benzyl group optionally substituted by one or two substituents selected from a) to h) as defined above, or a group of formula

wherein R_2 is as above defined, with a compound of formula (V)

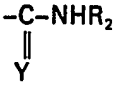


(V)

wherein R_6 and R_7 are as defined above, to form a compound of formula (I) in which R_5 represents a linear or branched C_1–C_4 alkyl or C_2–C_4 alkenyl group, a C_3–C_7 cycloalkyl group, a benzyl group optionally substituted by one or two substituents selected from a) to h) as defined above, or a group of formula

and optionally converting the resultant compound of formula (I) wherein R_5 either represents a benzyl group optionally substituted by a p-nitro or p-methoxy group or represents a group of formula

into a compound of formula (I) wherein R_5 is a hydrogen atom, a group of formula $-COR_2$ or

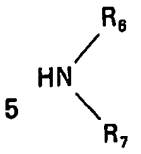


wherein Y and R_2 are as defined above, by deprotection and subsequent optional reaction with a compound of formula R_2COX or $Y=C=N-R_2$ wherein R_2 and Y are as defined above and X represents a halogen atom, preferably chlorine, bromine or iodine; and optionally converting a compound of formula (I) thus obtained into a pharmaceutically acceptable acid addition salt thereof.

Methods to get an amide linkage known to those skilled in the art may be used to obtain the desired amides (I) from the compounds (IV) and (V) (see, e.g., Y.S. Klausner and M. Bodansky, Synthesis *1972* 453; Houben-Weyl, Methoden der Organischen Chemie, Vol. 15/II, p.1, 1974).

For example, the acid (IV) can be dissolved in a dipolar aprotic solvent, preferably anhydrous dimethylformamide, in an inert atmosphere and treated with a small excess of carbonyl diimidazole usually within a temperature range of 25°–100°C until any evolution of carbon dioxide has ceased and the imidazolide formation is complete.

After treating the reaction mixture with the appropriate compound

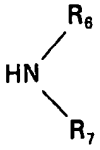


(V),

usually at room temperature, the amide (I) can be isolated through the usual work-up.

Alternatively, activation of the carboxylic acid (IV) can be achieved by dissolving it in a dipolar aprotic solvent, preferably anhydrous dimethylformamide or diglyme, adding stoichiometric amounts of dicyclohexylcarbodiimide and 1-hydroxy-benzotriazole, and a catalytic amount of 4-dimethyl-aminopyridine.

After stirring at room temperature, the mixture is treated with the amino component

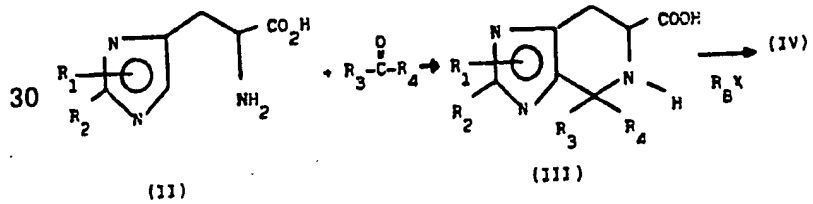


(V),

and the product (I) can be eventually isolated after conventional work-up.

In other cases, the methyl or ethyl esters of acids (IV) can be treated in an autoclave with methanolic or ethanolic solutions of the compounds (V). After heating at 50°–100°C for 1–3 days, the amide (I) can be purified by chromatography or crystallization.

The compounds of formula (IV) may be prepared according to the following synthesis diagram:

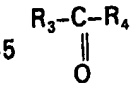


(II) (III)

wherein R_1, R_2, R_3, R_4, R_8 and X are as defined above.

Conversion of compound (II) into compound (III) is carried out in a solvent such as methanol, ethanol, n-butanol, in the pesence of aqueous alkali, usually at the reflux temperature of the mixtures.

When R_8 represents a benzyl group, the compound of formula (IV) may also be prepared by reaction between N-benzyl histidine optionally substituted, and an appropriate carbonyl compound of formula



as defined above. When R_8 represents an alkyl, alkenyl or cycloalkyl group, the compound of formula (IV) may alternatively be prepared according to T. Vitali et al. Gazz. Chim. Ital. *94*, 296 (1964). The compounds of the invention are useful in methods of treatment of the human or animal body by therapy. They have antiviral activity and can be used against RNA viruses in humans and other mammals. For this purpose, they can be formulated into oral dosage forms such as tablets, capsules and the like.

The present invention provides a pharmaceutical composition comprising as active ingredient a compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof, together with a pharmaceutically acceptable carrier or diluent.

The compounds can be administered alone or by combining them with conventional carrier or diluent, such as magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, low melting wax, cocoa butter, and the like. Flavoring agents, solubilizers, lubricants, suspending agents, binders, tablet-disintegrating agents and the like may be employed. The compounds may be encapsulated with or without other carriers. In all cases the proportion of active ingredients in said compositions both solid and liquid will be at least sufficient to impart antiviral activity thereto on oral administration. The compounds may also be injected parenterally, in which case they are used in the form of a sterile solution containing other solutes, for example, enough saline or

glucose to make the solution isotonic. Typically, a dose of 100–2000mg of a compound of the invention may be administered per day to a human under treatment.

The antiviral activity of the compounds of the invention may be demonstrated in standard procedures which are more fully described hereinafter. Anti-viral activity of compounds (I) was assessed both in "in vitro" and "in vivo" tests.

"In vitro" tests were carried out on monolayers of Hep#2 cells infected with herpes simplex virus, of BHK 21 cells infected with influenza virus, of dog kidney cells infected with infectious canine hepatitis virus (adenovirus), according to the Herrmann's paper disk test on agarized medium. The antiviral activity was determined, after either neutral red or tetrazolium staining, as halos of protection, i.e. as areas free of lysis plaques. The activity index (A.I.) was determined as the quotient: Activity halo diameter/Cytotoxicity halo diameter. In addition, human amniotic cells infected with rhinovirus were treated with scalar dilution of the present compounds in liquid medium; the antiviral activity was evaluated by microscopical observation of decreased cytopathic effect in comparison with the untreated-infected controls.

The A.I. was determined as the quotient: Concentration causing two cross toxicity effects (tox. 50%)/Minimal concentration exerting an antiviral activity (MIC). Results for some compounds of the present invention are shown in Table I, column 1.

In further "in vitro" studies, cytotoxicity was evaluated as the concentration of the drug which determines a 50% decrease of cellular growth (T.C.I.D.50), and the activity on infectious virus production was determined as the dose which reduces by 50% the titre of virus in cellular cryolysates (I.V.I.D.50). Results are shown in Table I, columns 2 and 1.

The approximate acute toxicity (LD_{50}) of the compounds of this invention was determined in the mouse by a single oral administration of increasing doses and measured on the seventh day after treatment. Results are reported in Table I, column 3.

Compounds selected for their low acute toxicity and for the activity shown in the "in vitro" tests, were studied by "in vivo" tests too, on influenza virus experimental infection in mice. It is known that influenza viruses, injected intranasally, induce in mice a pneumonia whose severity depends on the inoculum size: high doses cause death, low doses induce lungs lesions whose extension can be evaluated by scores. The antiviral activity of the present compounds, injected according to different schedules, was evaluated by the decrease of lesions and of virus titre in lungs in comparison with the infected controls. Results for the most active compound (FCE 20028, Table I, Example 3) orally administered (p.o.), are reported in Tables II and III.

TABLE I

"In vitro" biological activity and acute toxicity of selected compounds of the present invention Formula (I):

Code number	Example	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Column 1 A.I. (1) Herpes simplex	Adeno-virus	Influ-enza	Rhino-virus	Column 2 T.C.I.D.$_{50}$ (2)	Column 3 LD_{50} (3)
386/1585	12	H	H	H	H	H	H	C_6H_5	<1	2.2	3(10.5)	<1	160	>800
386/1710	11	H	H	H	H	$COOCH_2C_6H_5$	$(CH_2)_2$-N-$(CH_2)_2$ 		<1	<1	<1	2(3.2)	10	>200 <400
FCE 20027	10	H	H	H	H	CH_3	$(CH_2)_2$-N-$(CH_2)_2$ 		<1	<1	6(6.5)	4(7.0)	26-44	>800
FCE 20028	3	H	H	H	H	H	$(CH_2)_2$-N-$(CH_2)_2$ 		<1	1.5(12.5)	>4(12.5)	>2(70.0)	1100	>1400
FCE 20068	9	H	H	H	H	CH_3	$(CH_2)_2$-N-$(CH_2)_2$ 		<1	>4(25)	2(50.0)	<1	510	>800
FCE 20435	8	H	H	H	H	$COOCH_2C_6H_5$	H	H	<1	<1	4(40.0)	<1	100	>800
FCE 21762	7	H	H	H	C_2H_4	$CH_2C_6H_5$	H	H	<1	<1	<1	4(20.0)	100	>400 <800
FCE 23715	4	H	H	H	H	$COOCH_2C_6H_5$	H		<1	<1	6(2.5)	10(1.25)	12.5	-
REFERENCE COMPOUNDS : 1-Amino-adamantane (Symmetrel (R))									<1	<1	4(3-5)	<1	20-30	1080
Ribavirin (Virazole (R))									3	-	4(10)	2(12.5)	10-72	200
Inosiplex (Viruxan (R))									?	<1	4(100)	<1	510-640	>1000

(1) In brackets I.V.I.D.$_{50}$ (µg/ml)

(2) Expressed in µg/ml

(3) mg/kg p.o. in the mouse.

TABLE II

ANTIVIRAL ACTIVITY OF FCE 20028 ON MICE EXPERIMENTAL INFECTIONS WITH INFLUENZA VIRUSES

(% protection on lung lesions)

Schedule			Virus strain		
No. treat.	Time (day)	mg/kg p.o.	APR8	A_1FM_1	A_2W_{29}
1	+1	200	37	44	67
		100	47	37	23
		50	66	34	nd
1	+2	200	33	26	39
		100	36	29	41
		50	32	26	nd
5	+0→+4	100	25	37	nd
Reference compounds: RIBAVIRIN (VIRAZOLE (R)):					
1	+1	100	27	nd	50
5	+0→+4	50	41	nd	nd
		25	50	nd	33
INOSIPLEX (VIRUXAN (R)):					
2	+1	400	nd	22	nd
2	+2	400	nd	26	nd

nd: not determined

TABLE II

ANTIVIRAL ACTIVITY OF FCE 20028 ON MICE EXPERIMENTAL INFECTIONS WITH INFLUENZA VIRUS (APR8 STRAIN)

Schedule			% Protection	
No. treat.	Time (day)	mg/kg p.o.	Lung lesions	Lung virus titer
2	+0	100	61	99.6
2	+1	100	58	70
2	+2	100	35	0
Reference compound: INOSIPLEX (VIRUXAN (R)):				
2	+0	300	52	80
2	+1	300	0	0

The present invention is illustrated by the following examples:

EXAMPLE 1

5-Benzyloxycarbonyl-6-carboxyl-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine.

To an iced solution of NaOH(38g) in water (290 ml), dioxane (100 ml) and 6-carboxy-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine (78g; see T. Vitali and G. Bertaccini, Gazz. Chim. Ital. *94*, 296 (1964)) are successively added with cooling and stirring.

Benzyl chloroformate (135 ml) is then added dropwise over a period of 6 hours while the pH is maintained within the range 8.5 + 10.5. The ice-water bath is removed, the reaction mixture is allowed to stand overnight and then made strongly alkaline with 10N NaOH. The aqueous phase is washed with methylene chloride (2 × 200 ml) and then slowly acidified by adding 6N HCl dropwise. The white precipitate is washed with water and dried, affording 82 g of the pure title compound (m.p. 240°C).

EXAMPLE 2 (386/1707)

5-Benzyloxycarbonyl-6-(4'-phenyl-1'-piperazinocarbonyl)-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine.

To a suspension of 5-benzyloxycarbonyl-6-carboxyl-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine (3.013 g, 10 mmole) in anhydrous dimethyl formamide (30 ml), carbonyldiimidazole (1.78 g, 11 mmole) is added with stirring. After heating at 100°C over a period of 45 minutes, the reaction mixture is cooled at room temperature. N-phenylpiperazine (1.6 ml) is added, the solution is stirred overnight and eventually evaporated to dryness. Water (50 ml) and methylene chloride (50 ml) are added to the residue, the aqueous phase is repeatedly extracted and then discarded, the organic extracts are dried and evaporated in vacuo.

The foamy residue is crystallized from acetonitrile affording 3 g of the pure title compound (m.p. 200°C).

EXAMPLE 3 (FCE 20028)

6-(4'-phenyl-1'-piperazinocarbonyl)-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine

A solution of 5-benzyloxycarbonyl-6-(4'-phenyl-1'-piperazinocarbonyl)-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine (3 g) in methanol (100 ml) is hydrogenated under a pressure of 2 atm of hydrogen at 50°C over a period of 2 hours with 10% Pd/C (400 mg). The catalyst is filtered off and the filtrate evaporated in vacuo. To the foamy residue, redissolved in methanol (40 ml), 5N hydrogen chloride in methanol (4.4 ml) is added and the precipitate collected, washed with methanol and dried, affording the pure title compound crystallized with 3 mole of HCl (m.p. 215°C) in 75% overall yield.

EXAMPLE 4 (FCE 23715)

5-Benzyloxycarbonyl-6-adamantylaminocarbonyl-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine.

A mixture of 5-benzyloxycarbonyl-6-carboxyl-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine (10 g), hydroxybenzotriazole (4.9 g), dicyclohexylcarbodiimide (7.5 g), dimethylaminopyridine (0.2 g), anhydrous dimethyl formamide (100 ml), is stirred at room temperature for 2 hours. Adamantanamine (5 g) is added, the stirring is maintained for 3 more hours, and the reaction mixture is finally allowed to stand for 3 days. The precipitate (dicyclohexylurea) is filtered off, and the filtrate evaporated to dryness.

To the residue, water (100 ml) and 2N HCl are added, and the aqueous phase is repeatedly extracted with CH_2Cl_2. The organic extracts are dried, and evaporated to dryness. To the residue, water (100 ml) and 2N NaOH are added, and the aqueous phase is repeatedly extracted with CH_2Cl_2. The organic extracts are dried, evaporated in vacuo, and the residue crystallized from absolute ethanol, affording 10 g of the pure title compound (m.p. 222°C).

EXAMPLE 5 (FCE 23727)

5-Benzyloxycarbonyl-6-adamantylmethylaminocarbonyl-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine.

Operating as in EXAMPLE 4, but using 1-adamantanemethylamine, the title compound (m.p. 216°C) is obtained in 40% overall yield.

EXAMPLE 6 (FCE 23728)

6-Adamantylmethylaminocarbonyl-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine

Operating as in EXAMPLE 3, but starting from 5-benzyloxycarbonyl-6-adamantylmethylaminocarbonyl-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine (EXAMPLE 5) and omitting the final treatment with hydrochloric acid, the pure title compound (m.p. 157°C) is obtained in 80% overall yield.

EXAMPLE 7 (FCE 21762)

4-Ethyl-5-benzyl-6-carboxamido-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine

To a solution of N-benzylhistidine(4.9 g; see V.N. Reinhold, Y. Ishikawa, D.B. Melville, J.Med.Chem. *11*, 258 (1968)) in water (11 ml) and methanol (88 ml), a solution of NaOH (3.2 g) in water (11 ml) is added with cooling and stirring. Propionaldehyde (4.5 ml) is added dropwise and the mixture is then refluxed overnight. Further propionaldehyde (4.5 ml) and NaOH (3.2 g) are added and the mixture is refluxed until no more starting material can be detected by TLC (MERCK silicagel 60 F_{254} TLC plates, using chloroform/methanol/30% aq.ammonia 65:45:20 as eluant system and the Pauly's spray reagent for spot visualization on chromatograms). The mixture is then acidified with 2N HCl and evaporated in vacuo. The residue is redissolved in water, the solution treated with active charcoal and percolated through a column of a weakly basic ion-exchanger (Amberlite(R) IR-45, 100 g, free-base form). The column is washed with water, ethanol, water and finally eluted with 2N HCl. The acidic eluate is evaporated to dryness affording 4-ethyl-5-benzyl-6-carboxyl-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine dihydrochloride as a white foam and pure by TLC, in 75% overall yield. To a solution of the last compound (43 g, 120 mmole) in methanol (400 ml), a solution of 96% H_2SO_4 (80 ml) in methanol (400 ml) is added dropwise with stirring and cooling (ice-salt bath). The solution is saturated with hydrogen chloride, allowed to warm to room temperature and refluxed till no more starting material can be detected by TLC (MERCK silica gel F_{254} TLC plates, using toluene/ethanol/ 35% aq. methylamine 6:3:1 as eluant system, and the Pauly's spray reagent for spot visualization on chromatograms). The solution is cooled and poured into a vigorously stirred mixture of 10% aq. Na_2CO_3, crushed ice and chloroform. The organic layer is separated, the aqueous phase thoroughly extracted with chloroform, the organic extracts combined, dried and evaporated in vacuo, affording 4-ethyl-5-benzyl-6-methoxycarbonyl-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine (30 g) as a colourless glassy oil pure by TLC. To a solution of the last compound (30 g) in methanol (1 liter), liquid ammonia (300 ml) is added, the solution is heated at 80°C in an autoclave for 3 days, then cooled and evaporated in vacuo. The residue is chromatographed on a silica gel column (MERCK 70–230 mesh ASTM silica gel, 1 kg) using chloroform with increasing methanol as eluant. The fractions containing the title compound are combined, evaporated in vacuo and the foamy residue taken up in a little chloroform (50 ml). 18 g of the pure title compound (m.p. 150°C) as white crystals are collected.

EXAMPLE 8 (FCE 20435)
5-Benzyloxycarbonyl-6-carboxamido-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine
Operating as in EXAMPLE 2, but using liquid ammonia as amino component, the pure title compound (m.p. 202–4°C) is obtained in 40% overall yield.

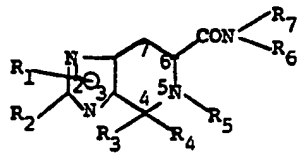
EXAMPLE 9 (FCE 20068).
5-Methyl-6-[4'-(p-methoxyphenyl)-1'-piperazinocarbonyl]-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine.
Operating as in EXAMPLE 2, but starting from 5-methyl-6-carboxyl-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine, and using 4-(p-methoxyphenyl)-piperazine as amino component, the pure title compound (m.p. 209–11°C) is obtained in 45% overall yield.

EXAMPLE 10 (FCE 20027)
5-Methyl-6-[4'-(p-chlorophenyl)-1'-piperazinocarbonyl]-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine.
Operating as in EXAMPLE 9, but using 4-(p-chlorophenyl)-piperazine as amino component, the pure title compound (m.p. 223–5°C) is obtained in 60% overall yield.

EXAMPLE 11 (386/1710).
5-Benzyloxycarbonyl-6-[4'-(p-chlorophenyl)-1'-piperazinocarbonyl]-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine.
Operating as in EXAMPLE 2, but using 4-(p-chlorophenyl)-piperazine as amino component the pure title compound (m.p. 170–2°C) is obtained in 60% overall yield.

EXAMPLE 12 (386/1585)
6-Phenylaminocarbonyl-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine.
Operating as in EXAMPLES 2 and 3, but using aniline as amino component and omitting the final treatment with hydrochloric acid, the pure title compound (m.p. 120–2°C) is obtained in 40% overall yield.

CLAIMS
1. A 4,5,6,7-tetrahydroimidazo[4,5-c]pyridine derivative of general formula (I):



(I)

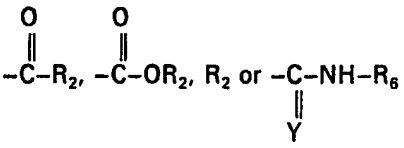
wherein

—R_1, which is bonded to the nitrogen atom in the 1- or 3- position, is a hydrogen atom; a linear or branched C_1–C_4 alkyl or C_2–C_4 alkenyl group; or a benzyl group optionally substituted by one or two substituents selected from a) C_1–C_4 alkoxy, b) C_1–C_4 alkylthio, c) fluorine, d) chlorine, e) bromine, f) trifluoromethyl, g) nitro, and h) methylendioxy;

—R_2, R_3 and R_4 are independently hydrogen; a linear or branched C_1–C_4 alkyl or C_2–C_4 alkenyl group; a C_3–C_7 cycloalkyl group; a phenyl or benzyl group optionally substituted by one or two substituents selected from a) to h) as defined above; or R_3 and R_4, together with the the carbon atom to which they are attached, form a C_3–C_7 ring;

—R_6 and R_7 are independently hydrogen; a linear or branched C_1–C_4 alkyl or C_2–C_4 alkenyl group; a C_3–C_7 cycloalkyl group; a phenyl or benzyl group optionally substituted by one or two substituents selected from a) to h) as defined above; an adamantyl or an adamantanemethyl group; or R_6 and R_7, together with the nitrogen atom to which they are attached, for a five-, six- or seven membered heterocyclic ring which may contain one or more other heteroatom selected from O and NR_2 wherein R_2 is as defined above; and

—R_5 represents a group of formula



wherein R_2 is as defined above but is not a phenyl group when R_5 is R_2, and Y represents an oxygen or sulphur atom;

and pharmaceutically acceptable acid addition salts thereof.

2. A compound according to claim 1 wherein R_1 and R_2 independently represent a hydrogen atom or a methyl ethyl, n-propyl, i-propyl, n-butyl, sec-butyl or i-butyl group;
R_3 and R_4 independently represent a hydrogen atom or a methyl, ethyl, n-propyl, i-propyl, n-butyl, sec-butyl, i-butyl, phenyl (optionally para-substituted by a methoxy or nitro group) group or, taken together, represent a cyclohexane or cyclopentane ring;
R_5 represents a hydrogen atom or a methyl, ethyl, n-propyl, i-propyl, n-butyl, sec-butyl, i-butyl, benzyl or benzyloxycarbonyl (either optionally being para-substituted by a methoxy or nitro group), benzoyl, butyryl, acetyl, propionyl, allyloxycarbonyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl, methylaminothiocarbonyl, ethylaminothiocarbonyl or propylaminothiocarbonyl group; and
R_6 and R_7 independently represent adamantyl, adamantanemethyl, hydrogen, phenyl (optionally substituted by fluorine, methoxy or trifluoromethyl) or, taken together, form a piperazino ring substituted by phenyl, p-methoxyphenyl or p-chlorophenyl or a morpholino ring.

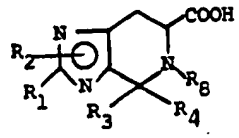
3. A compound according to claim 1, wherein R_1 and R_2 represent hydrogen, one of R_3 and R_4 represents ethyl or hydrogen and the other represents hydrogen, R_5 represents hydrogen, methyl, unsubstituted benzyl or benzyloxycarbonyl, and one of R_6 and R_7 represents adamantyl, adamantanemethyl, unsubstituted phenyl or hydrogen and the other represents hydrogen or R_6 and R_7, together with the nitrogen atom to which they are attached, form a piperazino ring substituted by phenyl, p-methoxyphenyl or p-chlorophenyl.

4. A compound according to claim 1 hereinbefore specified in any one of Examples 2 to 12.

5. A compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable acid addition salt thereof for use in a method of treatment of the human or animal body by therapy.

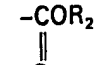
6. A compound of formula (I) or salt thereof according to claim 5 for use as an antiviral agent.

7. A process for preparing a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable acid addition salt thereof, which process comprises reacting a compound of formula (IV) or a reactive derivative thereof;

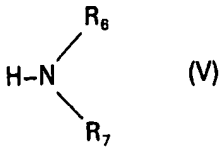


(IV)

wherein R_1, R_2, R_3 and R_4 are as defined in claim 1 and R_8 represents a linear or branched C_1–C_4 alkyl or C_2–C_4 alkenyl group, a C_3–C_7 cycloalkyl group, a benzyl group optionally substituted by one or two substituents selected from a) to h) as defined in claim 1, or a group of formula

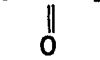


wherein R_2 is as defined above, with a compound of formula (V)

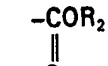


(V)

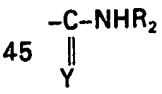
wherein R_6 and R_7 are as defined in claim 1, to form a compound of formula (I) in which R_5 represents a linear or branched C_1–C_4 alkyl or C_2–C_4 alkenyl group, a C_3–C_7 cycloalkyl group, a benzyl group optionally substituted by one or two substituents selected from a) to h) as defined in claim 1, or a group of formula



optionally converting the resultant compound of formula (I) wherein R_5 either represents a benzyl group optionally substituted by a p-nitro or p-methoxy group or represents a group of formula



into a compound of formula (I) wherein R_5 is a hydrogen atom, a group of formula $-COR_2$ or



wherein Y is as defined in claim 1 and R_2 is as defined above, by deprotection and subsequent optional reaction with a compound of formula R_2COX or $Y=C=N-R_2$ wherein R_2 and Y are as defined above and X represents a halogen atom; and optionally converting a compound of formula (I) thus obtained into a pharmaceutically acceptable acid addition salt thereof.

8. A process for the preparation of a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable acid addition salt thereof, said process being substantially as hereinbefore described in any one of Examples 2 to 12.

9. A pharmaceutical composition comprising as active ingredient a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable acid addition salt thereof, together with a pharmaceutically acceptable carrier or diluent.

Printed in the United Kingdom for Her Majesty's Stationery Office, Dd 8818935, 1985, 4235.
Published at The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.